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TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Review of "Profile of the Triazole-derivative Fungicide Compounds and their Common Metabolites" (MRID#: 45575501; DP Barcode: D284131)

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The Bayer Corporation, on behalf of the Triazolylalanine Group (TAG), submitted a document entitled, "Profile of the Triazole-derivative Fungicide Compounds and their Common Metabolites," (January 9, 2002). The stated intent of this document was to pull together in one place, all the toxicological, metabolism and residue data available to address the EPA's concern over exposure to triazole-derivative (T-D) fungicides. Included in the document is a cumulative acute dietary exposure and risk assessment of 1,2,4-triazole (including drinking water). While the entire document (566 pages) includes a number of tables, bibliographies, and discussions of data, the Agency believes that the most efficient and effective way to comment on the document is to focus its attention on the "overriding conclusions drawn by the TAG." These conclusions are listed on page 12 of the January 9th TAG document, and are repeated below, along with the Agency's response and comments.

Comment/Response for TAG Assessment

TAG Conclusion 1.

Of the three common metabolites of the T-D fungicides, only 1,2,4-triazole can be considered toxicologically significant. The plant metabolites, triazolylalanine (TA) and triazolylacetic acid (TAA), have been thoroughly assessed previously and, as then, the outcome remains the same: The toxicity of these metabolites is so low that their concern and contribution to any dietary risk would be insignificant despite the fact that they are the terminal residues in most crop matrices.

EPA Response 1.

HED disagrees that toxicity of triazole conjugates are not of concern. Although limited data available indicate that TA may be less toxic than free triazole:

– developmental toxicity was seen in the same range as for some parent triazole compounds;
– some available mutagenicity studies have found positive or equivocal results;
– the available toxicity database is very limited, in particular there are no chronic toxicity studies.

Therefore, we believe endpoints for free triazole should be used to assess risk from free triazole and conjugates, combined, until data are available supporting development of separate risk assessments.

Residue levels of some triazole conjugates are substantial given the toxicity findings described above. HED believes that these compounds need to be included in the risk assessment. In addition, it is possible that there may be interconversion between triazole conjugates and free triazole:

– in the environment
– during cooking and processing
– as a result of animal metabolism

In summary, the TAG, in its 1/9/02 revised assessment, continues to exclude conjugates of 1,2,4-triazole claiming they are not residues of toxicological concern of the triazole fungicides while acknowledging that these conjugates are the major components of the plant residue. This is one of the key flaws of their assessment the outcome being that exposure to only free triazole was estimated resulting in a great underestimation of dietary exposure. Even if reliable toxicity data demonstrate that triazole conjugates are less toxic than free triazole, a much higher exposure to a compound of lower toxicity may result in greater risk than low exposure to a compound of high toxicity.

TAG Conclusion 2.

The major portion of the contribution of free-triazole to the overall hazard/risk assessment of the parent T-D compound is fully covered by the bank of toxicology studies required to support registration of the parent compound, given that it is a common mammalian metabolite. Thus, the existing toxicology database on the parent T-D compound, when coupled with key triazole-labeled metabolism and environmental fate data, would be sufficient to allow the Agency to adequately perform hazard/risk assessments of the triazole-derivative fungicide compounds.

EPA Response 2.

EPA disagrees that the toxicity profile of free triazole is adequately addressed by the data provided in the toxicology databases for the parent triazole pesticides, for the following reasons:

1) Although free triazole does appear to be a common mammalian metabolite for some triazole pesticides, the proportion of parent compound appearing as free triazole in metabolism studies is variable, and for the most part small. In addition, metabolism studies in which the triazole ring was labeled are unavailable for some pesticides, so the proportion of free triazole could not be determined for those compounds. For example, a survey of available metabolism studies for14 T-D pesticides found:

– for 5 pesticides, triazole-labeled studies were not available;
– for 3 pesticides, no free triazole was detected;
– for 5 pesticides, free triazole represented 4-18% of administered dose;
– for 1 pesticide, free triazole represented approximately 67% of administered dose.

2) Because free triazole represents a small and variable proportion of the metabolites for triazole pesticides, and because the toxicity of the parent compounds is also variable, it is not possible to allocate the toxicity seen in any given study among the parent compound and its metabolites.

3) Because the free triazole is formed during metabolism, exposure of various organs to free triazole following administration of parent compound is different than would occur following direct administration of free triazole. In addition, concurrent exposure to parent compound and free triazole may modify the toxicity of the free triazole, due to possible interactions at various target organ sites.

4) Exposure to free triazole is not included in current risk assessments for parent triazole pesticides. In order to estimate risk/hazard from direct exposure to free triazole, it will be necessary to use toxicity endpoints based on exposure of animals to free triazole. The current toxicity database for free triazole is very limited, and is not adequate for assessing hazard from long-term exposure, of the type expected based on current exposure information.

TAG Conclusion 3.

The contribution of 'extraneous' free-triazole, i.e. obtained indirectly via the ingestion of meat, milk and eggs, and from driking water, is compound-specific. Therefore, key radiolabeled studies (i.e. labeled on the triazole ring) would be necessary to define the magnitude of the compound-specific release of free-triazole in order to fill the gaps for the risk assessment exercise. However, as these are all T-D compound specific, they should only be considered in the context of the pertinent T-D compound's assessment of hazard and risk.

EPA Response 3.

While the first statement is likely to be correct, the Agency is now required by law to consider all sources of exposure when conducting aggregate risk assessments for the establishment of tolerances. Therefore, all sources of free triazole need to be included when assessing the risk for a food-use fungicide that produces this metabolite/degradate. In those cases where the fungicide does not produce measurable residues of free triazole (e.g., some seed treatments) or the use is non-food and does not lead to residues in drinking water (e.g., greenhouse use), the Agency may be able to proceed without considering other sources of triazole.

TAG Conclusion 4.

The residue levels of 1,2,4-triazole in food commodities are very low and are observed in only 15 %, or less, of crop matrixes. As such, their contribution to the dietary load of extraneous free-triazole is low. The need to incorporate them into crop residue definitions is therefore unnecessary.

EPA Response 4.

With respect to the last statement, the Agency is likely to concur if the registrants are referring to the residue definition for tolerance enforcement purposes. Free triazole would not be a good indicator of pesticide misuse due to its numerous sources. However, from a risk assessment perspective, the free triazole residues as well as those of its conjugates need to be included based on the toxicological properties of these compounds. The available radiolabeled studies appear to support the first statement, at least with respect to crops in their raw agricultural state (residues are detected in a small fraction of plant samples and are at levels <0.1 ppm). However, it is not known whether food processing converts residues of the parent fungicides or the triazole conjugates to free triazole. Taking into account that uncertainty and the fact that exposure is a function of residue level and consumption, it is not possible at this time to conclude whether or not plant sources of free triazole residues to the diet are significant in comparison to the other sources (livestock commodities, drinking water). The Agency believes that the best way to assess dietary exposure to triazole and its conjugates would be to conduct a market basket survey.

Additional EPA Comments on the TAG Assessment

Toxicology:

The TAG assessment used the NOAEL of 30 mg/kg/day from a developmental study with free triazole for dietary risk assessment. This is the endpoint selected by HED for use in the interim risk assessment. However, we note that the database is minimal, in particular with no long term studies of any sort; therefore, this endpoint may be changed as additional data become available.

The TAG assessment removed the FQPA safety factor (used 1x). There is no basis for removing the FQPA safety factor for this risk assessment. HED selected a total UF (to include FQPA issues) of 1000 for use in the dietary risk assessment. The need for an additional 10x is supported by:

– Major data gaps (no chronic studies, limited developmental and reproduction studies, etc.)

– Structure-activity analogies with related compounds, including parent triazole compounds, raise the likelihood that free triazole and its conjugates may affect endocrine systems; many parent T-D compounds cause developmental toxicity and effects were seen in available developmental toxicity studies for free triazole and triazole alanine. In addition, many parent T-Ds are carcinogens (and some of the mutagenicity studies for triazole alanine were positive/equivocal), but no carcinogenicity studies are available for free triazole or triazole conjugates.

Dietary:

Another potentially great underestimation of dietary exposure results from the TAG approach of predicting free triazole concentrations in foods and feeds based on the amount of the parent fungicide compound at harvest using a plant metabolic conversion rate and a molecular weight conversion factor. While the conversion rate and conversion factor used were claimed to be worst-case, this approach fails to include the triazole conjugates (formed in the plant or taken up from the soil) and may also not account for free triazole taken up by the plant from the soil. As the triazole ring is quite stable, the soil is expected to serve as a major reservoir of plant residues, i.e., free triazole and its conjugates tend to increase in crops with time over a season, they may accumulate in soil and crops following repeat applications, and they may even recycle back into the soil upon incorporating crop wastes.

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The TAG assumed that 100% of each crop was treated and default processing factors as conservative measures to permit the conduct of a Tier 1 assessment. HED agrees with the use of 100% crop treated but we are not certain how conservative it is; crop rotation, land ownership changes, and the persistence, mobility, and accumulation of the triazole ring in soil and crops render quite difficult the estimation of the percent of any given crop being grown on or near land that has not recently been treated with a triazole fungicide. Risk at the 95th percentile of exposure is appropriate for a Tier 1 assessment. Of course, if exposure refinements are conducted, a higher percentile of exposure will be necessary for risk estimation.

In summary, with all the uncertainties, HED is unable to determine how accurate the TAG assessment is for residues of **free** triazole. Regardless of that, total exposure to the residues of concern (free **plus** conjugated triazole) is likely to be significantly higher than the TAG's estimate for free triazole alone.

Drinking Water Exposure Assessment:

Although the approach to the drinking water assessment seems reasonable, there are a number of questions and uncertainties in the selection of the triazole modeling input parameters and "application rate". Furthermore, if there are human health concerns for the triazole conjugates (triazolylalanine and triazolylacetic acid), these may need to be included in the drinking water assessment.

1. The drinking water assessment was performed only on 1,2,4-triazole. The assessment did not include TA and TAA. However, triazolylacetic acid has been identified in at least one study for one of the T-D compounds (tetraconazole).

In the tetraconazole photodegradation on soil study, both 1,2,4-triazole and TAA were formed at the maximum of 3.7% and 4.9% of the applied (112 days PPT, the last sampling interval), respectively (MRID 44367004). If TAA is of human health concern it should be included in the drinking assessment. If TA was detected in any laboratory or/and field studies it may need to be assessed as well.

2. The maximum percent formation rates of triazole metabolites observed in the soil metabolism studies (ranges from 9% to 30.7% of the parent) were used to derive the triazole "application rate" for the drinking water modeling.

The data are for the laboratory studies only.

A) The formation rate of triazole from tetraconazole in the field dissipation studies is, however, not known and may be highly uncertain from tebuconazole.

Tetraconazole degradates were not analyzed in any of the registrant-submitted field dissipation studies. Tebucanozole field dissipation studies indicate that 1,2,4-triazole was not stable during transport and storage. When soil samples were fortified with 1,2,4-triazole at 1.0 ppm (MRID 44108315; 164-1), mean recoveries were 0.84-0.90 μg/g for samples stored for 273-422 days, 0.71-0.72 μg/g for samples stored for 509-633 days, and 0.51-0.53 μg/g for samples stored for 770-804 days post-treatment. Samples analyzed for 1,2,4-triazole were stored frozen for up to 893 days prior to analysis. The lack of 1,2,4-triazole stability in soil samples adds to the uncertainty of the field analysis for this degradate.

B) The formation rate of triazole is not known for persistent T-D compounds - for example, bromuconazole.

Bromuconazole is so persistent (field half-lives of 7.3 to 13.8 months) that, in many studies there was insufficient time for many metabolites to appear in major quantities. Although it appears from these studies that the triazole is not easily separated from the parent compound, these studies also do not provide any direct proof that triazole, TA, and TAA were not formed under the test conditions.

3) Free-triazole soil half-life in laboratory studies ranged from 7-81 days for initial concentrations of 1 ppm or less, with major route of degradation by hydroxylation.

EFED does not have enough confirming evidence that triazole residues in the field would not exceed the level of 1 ppm in agricultural soils. The EFED-calculated half-life values range from 22 to 155 days for concentrations of 1 ppm or less and 343-375 days for the higher concentration of 50 ppm. The aerobic soil metabolism degradation products were hydroxytriazole (3-hydroxy-1,2,4-triazole), triazolylalanine (1,2,4-triazole-1-alanine), and triazolylacetic acid, CO_2, and bound residues.

4) Median half-life value of free-triazole and the smallest Koc value was used in SCI-GROW groundwater model.

The approach is not conservative because not all half-lives were considered for the calculation of the median aerobic soil metabolism value. A conservative approach seems more appropriate considering the uncertainty associated with the maximum amount of free triazole present in the soil. For Koc, a median value of 104 L/Kg is suggested.

5) The upper 90% confidence limit on the mean value of the aerobic soil metabolism half-lives was used and the aerobic aquatic half-life was calculated as 2x the aerobic soil half-life for inputs into the surface water modeling.

EFED believes that a more conservative approach should be taken. The upper 90% confidence limit on the mean value of the aerobic soil metabolism half-lives of all valid half-life values should be used. EFED calculated the upper 90% confidence limit on the mean value of the aerobic soil metabolism half-lives as being 250 days. Doubling the value would yield an aerobic aquatic half-life of 500 days, according to current input parameter guidelines ("Guidance for Selecting Input Parameters in Modeling the Environmental Fate and Transport of Pesticides" Dec 4, 2001).

6) The lowest non-sand Koc value was used in the FIRST modeling.

To estimate the dissolved and the adsorbed fraction of 1,2,4-triazole, the lowest non-sand texture soil K_f value should be used (sandy loam: $K_f = 0.72$) because the Freundlich adsorption coefficient may not be an adequate representation of adsorption across all concentrations and it cannot be assumed that K_f is equal to K_d (1/n = 0.827-0.897 for the silty clay, clay loam, and sand soils). Furthermore, there was no linear relationship between the K_d values and the soil organic matter content over a 0.1 to 0.005 ppm concentration range ($r^2 = 0.40$). Therefore, the organic carbon model may be not valid.

7) Used worst-case Drinking Water Estimated Concentration (DWEC) of 32.1 ppb in assessment.

The reported EEC of 32.1 ppb for surface water may be underestimated. The presented scenario has too many uncertainties and may not be a "worst case" scenario for a drinking water assessment of free triazole. The formation of TA and TAA were not considered in the presented drinking water assessment and the modeling input parameters may not be conservative enough. Additionally, formation of triazole from persistent T-D compounds was not addressed.

The authors reported the 1,2,4-triazole maximum ground water concentration as being 16.7 ppb, much higher than the estimated environmental concentration (EEC) of 0.026 ppb. This indicates that the ground water EEC value was not conservative.

Data from a Prospective Ground Water study conducted in NJ after two applications of triadimefon (BAYLETON) to turf (Dyer and Helfrich, 1999) indicate the possibility of triazole accumulation in pore water. The maximum concentration of free triazole in soil pore water at 9 ft depth (maximum depth) was 36.2 ppb. Average triazole concentrations in pore water at 9 feet depth increased to approximately 14 ppb by 486 days and remained at this level until the end of the sampling, 659 days, showing lack of apparent decline. This may indicate a possibility of triazole accumulation in pore water due to successive application of persistence and non-persistent T-D compounds in rotation year to year.

Occupational and Residential Exposure:

The use of triazole-derivative fungicides may result in dermal and inhalation exposure from occupational and residential application, and in dermal and incidental oral exposure (toddlers) from contacting residues after application has been made. Exposure from application activities is assumed to be primarily to the parent triazole compound. Postapplication exposure, however, could be to residues of the parent compound, as well as to metabolic breakdown products (i.e., free triazole, TA or TAA) in the soil and perhaps on the foliage in treatment areas. The presence and extent of free triazole and triazole conjugates (particulary on treated foliage) is not known. Without a dislodgeable foliar residue study, any occupational and residential postapplication exposure/risk assessment would have to be performed with OPP standard values and assumptions for amounts of residues initially available to be dislodged and for the amount of dissipation of residues over time.

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